IOSR Journal of Applied Chemistry (IOSR-JAC)
e-ISSN: 2278-5736.Volume 11, Issue 7 Ver. I (July. 2018), PP 57-62
www.iosrjournals.org

Synthesis Of Thiophene Isoxazolines In Ionic Liquid [Bmim][BF_4]

Priyanka C. Burde*, Anjali M. Rahatgaonkar*
**Department of Chemistry, Institute of Science, Civil Lines, Nagpur 440001*
Corresponding Author: Priyanka C. Burde

Abstract: *[BMIM][BF_4] was used as an efficient ionic liquid for the synthesis of thiophene isoxazolines through the cyclocondensation of α,β-unsaturated thiophene ketones with hydroxylamine hydrochloride in ionic liquid/water/acetic acid biphasic system at 80°C temperature. The methodology puts forward several rewards such as exceptional yields, easy method and mild conditions.*

Keywords*: Thiophene isoxazolines, [BMIM][BF_4], biphasic system, α,β-unsaturated thiophene ketones*

Date of Submission: 26-06-2018 Date of acceptance: 11-07-2018

I. Introduction

Isoxazoles are well known five membered heterocyclic compounds, receiving considerable importance both inadvance organic material[1] and biological applications in medicinal[2] and material science[3]. Isoxazole derivatives are a promising structural moiety for drug designing, which are reported to possess antibacterial, anticonvulsant, antipsychotic, anti- inflammatory, antitumor, analgesic, insecticidal, antioxidant, anti depressant and anti microbial activities. [4-12]

The most representative synthetic strategies for the construction of isoxazoles nucleus including (i) reaction of hydroxylamine with 1,3dicarbonyl compounds[13] (ii) [3 + 2] cycloaddition of alkynes/ alkenes and nitrile oxides[14] (iii) intermolecular cyclization of oximes with C−C double/triple bonds[15]. However; these synthetic strategies generally require harsh reaction condition including strong bases, strong mineral acids, or high temperatures or provide modest regioselectivity and neither economic nor eco-friendly.

Ionic liquids (ILs) have been extensively promoted as well-designed replacements of volatile organic solvents; however limiting their use to conventional solvents restrict their potential. The impact of Ionic liquids in chemistry is associated to their exceptional properties as non-molecular solvents: a negligible vapor pressure associated to a high thermal stability. The emergent significance of ionic liquids (ILs) has resulted in an exponentially increasing invention of synthetic and analytical applications.

Ionic liquids (ILs) have been accepted as a new green chemical revolution which excited both the academia and the chemical industries. This new chemical group can reduce the use of hazardous and polluting organic solvents due to their unique characteristics as well as taking part in various new syntheses.The terms room temperature ionic liquid (RTIL), nonaqueous ionic liquid, molten salt, liquid organic salt and fused salt have all been used to describe these salts in the liquid phase[16]. ILs are known as salts that are liquid at room temperature in contrast to high-temperature molten salts. They have a unique array of physico-chemical properties which make them suitable in numerous applications in which conventional organic solvents are not sufficiently effective or not applicable. Researchers have discovered that ILs are more than just green solvents and they have found several applications such as replacing them with volatile organic solvents, making newmaterials, conducting heat effectively, supporting enzyme-catalyzed reactions, hosting a variety of catalysts, purification of gases, homogenous and heterogeneous catalysis, biological reactions media and removal of metal ions[17]. [bmim][BF4], hydrophilic ionic liquid is well known for its capability in various catalytic applications. Particularly, hydrophilic media possessing tetra fluoroborate [BF_4] anions have a multitude of usages in different biochemical and chemical reactions.[18] Chaban and Prezhdo[19] *et al* investigated the volatility of the imidazolium-based RTILs/ACN mixtures on the basis of precision simulations of liquid/vapor interfaces over a wide composition range and observed noticeable decrease in the volatility of ACN, and hence, reduced hazards.

Kumar V. Srinivasan *et.al* [20] described an improved and rapid one-pot synthesis of 2,4,5-triaryl imidazoles in a room temperature ionic liquid, which does not need any added catalyst.

We embarked on the synthesis of thiophene isoxazoles via the cyclocondensation of α,β-unsaturated thiophene carbonyl compounds with hydroxylamine hydrochloride. A number of solvent systems have been investigated to set the reaction conditions of these compounds. In the said synthesis, we have chosen 3-(thiophen-2-yl)-1-p-tolylprop-2-en-1-one (**1a**), as a starting material. We have made efforts in making a library

of isoxazolines using different concentration of [BMIM][BF_4], in biphasic solvent system and our observations prompted us to explore the potential use of [BMIM][BF_4], /water solvent system.

II. Materials and Methods

Material and Methods:

Chemicals used were of analytical reagent grade. All the solvents were dried and freshly distilled prior to use. Thin layer chromatographic analysis was performed on precoated silica gel plates (Alugram® SIL G/UV_{254}, 0.2mm thickness). Melting points were recorded by open capillary method and are uncorrected. Infrared (IR) spectra were recorded on FT-IR Spectrometer. Proton magnetic resonance (^{1}H-NMR) spectral data were recorded on a Bruker 400MHz spectrometer in DMSO-d_6 solution. The chemical shifts are reported in δ (ppm) relative to internal standard tetramethylsilane (TMS) and coupling constant J is given in Hz. Mass spectrometry was conducted using WATERS,Q-TOF MICROMASS.

General Procedure:

A conventional method: A mixture of differently substituted chalcones (**1a-e**), 3-(thiophen-2-yl)-1-(p-substituted)prop-2-en-1-ones (10mmol) were dissolved in 20 ml of ethanol along with hydroxylamine hydrochloride (10mmol) in acetic acid were refluxed for 6 hours. The reaction mixture was then poured into ice cold water with stirring and left over night at room temperature. The progress of the reaction was monitored by TLC.The precipitate obtained was filtered, washed and dried. The products 3-cyclopropyl-5-(p-substituted)-4,5-dihydroisoxazole (**3a-e**) were recrystallised using ethanol. Similar procedure was followed for various chalcones.

Preparation of 3-(thiophen-2-yl)-5-(p-tolyl)-4,5-dihydroisoxazole:**3a**: $C_{14}H_{13}NOS$

A mixture of (E)-1-cyclopropyl-3-(p-tolyl) prop-2-en-1-one, (10mmol) **1a** and hydroxylamine hydrochloride (10mmol) was introduced into a vigorously stirred [bmim][BF_4] (10 mmol) and water (10 mmol)/acetic acid(10mmol) biphasic solvent system at room temperature for 2 h. The temperature of the reaction mixture was maintained at 80^{o}C. TLC was not feasible as the reaction mixture contained ionic liquid. After completion, the reaction was quenched with water (5mL) and the product was seperated out by extracted with diethyl ether (10 mLx3). The ionic liquid [bmim]BF_4] layer was dried over the anhydrous $CaCl_2$ in a descicator and later on it was oven dried with prior to use. The organic layer was dried over anhydrous Na_2SO_4 and then concentrated in vacuo to afford pure 3-cyclopropyl-5-(p-tolyl)-4,5-dihydroisoxazole **3a**. The product was recrystallized from ethanol. The oven dried ionic liquid has been reused for next reaction without noticeable effect on the reaction.
$C_{14}H_{13}NOS$: Yield:95% ,Melting Point:123° C, IR (KBr, λ_{max}/cm^{-1}): 1657(C=N),1804 (N-O), 3040(Ar-H), 1097 (C-O), 2466(CH_2 iso)cm^{-1} , ^{1}H NMR(400 MHz, $CDCl_3$ /DMSO-d6): δ(ppm) 2.35 (s, 3H, Ar-CH_3); 2.80-J=8.36, 8.36Hz, H_d); 1.87-1.95 (dd, 1H, J=1.72, H_e); 7.00-7.02 (dd, 1H, J=3.56-3.6, H_f); 7.13-7.28 (m, 3H,Thiophene ring); 7.32-7.57 (m, 4H, phenyl ring). ^{13} C NMR (200MH_Z $CDCl_3$) : δ 21.48, 42.84, 83.08, 124.21, 125.31, 127.94, 129.99, 137.02, 139.00, 161.99;Mass Spectrum : m/z 243 M$^+$, 228, 160, 152, 91, 83 ; CHN calculated : C 69.11, H 5.39, N 5.76; CHN found: C 69.09, H 5.37, N 5.74

Preparation of 5-(4-bromophenyl)-3-(thiophen-2-yl)-4,5-dihydroisoxazole:**3b**: $C_{13}H_{10}BrNOS$

Yield: 92 %,Melting Point: 117℃, IR (KBr, λ_{max}/cm^{-1}): 1650(C=N),1798 (N-O), 3047(Ar-H), 1068 (C-O), 2467(CH_2 iso)cm^{-1} , ^{1}H NMR(400 MHz, $CDCl_3$ /DMSO-d6): δ(ppm)= 2.99-3.07 (dd,1H, J=8.36,11.48Hz, H_d); 2.12-2.20(dd, 1H, J=8.28,11.36Hz, H_e) ; 6.80-6.99 (m, 1H, H_f);7.03-7.22(m,3H, Thiophene ring); 7.31-7.71 (m, 4H, phenyl ring), ^{13} C NMR (200MH_Z $CDCl_3$) : δ42.28, 83.48, 121.83, 124.16, 125.47, 127.33, 131.89,141.65, 163.05, Mass Spectrum: m/z 308M$^+$, CHN calculated: C 50.66, H 3.27, N 4.54, CHN found : C 50.64, H 3.25, N 4.52

Preparation of 5-(4-chlorophenyl)-3-(thiophen-2-yl)-4,5-dihydroisoxazole:**3c**: $C_{13}H_{10}ClNOS$

Yield: 95% ,Melting Point: 127℃, IR (KBr, λ_{max}/cm^{-1}): 1652(C=N), 1797 (N-O), 3049(Ar-H), 1095(C-O), 2468(CH_2 iso) cm^{-1} , ^{1}H NMR(400 MHz, $CDCl_3$ /DMSO-d6): δ(ppm) 2.74-2.81 (dd, 1H, J=8.28,11.6 Hz,H_d); 1.87-1.95 (dd, 1H, J= 8.28,11.6Hz,H_f); 6.84-6.91 (m, 1H, H_f);6.97-7.13 (m, 3H, Thiophene ring); 7.16-7.42 (m, 4H, phenyl ring), ^{13} C NMR (200MH_Z $CDCl_3$) : δ42.99, 83.34, 122.41, 124.99, 126.85, 127.91, 129.42, 134.00, 140.00, 164.11, Mass Spectrum: m/z 263M$^+$, CHN calculated: C 59.20, H 3.82, N 5.31, CHN found : C 59.18, H 3.80, N 5.29

Preparation of 5-(4-fluorophenyl)-3-(thiophen-2-yl)-4,5-dihydroisoxazole:**3d**: $C_{13}H_{10}FNOS$

Yield: 95%,Melting Point:161℃, IR (KBr, λ_{max}/cm^{-1}): 1657(C=N), 1798(N-O), 3051(Ar-H), 1094(C-O), 2441(CH_2 iso)cm^{-1}, ^{1}H NMR(400 MHz, $CDCl_3$ /DMSO-d6): δ(ppm) 2.90-2.97 (dd, 1H, J=8.16,11.56Hz, H_d);

2.02-2.09(dd, 1H,J= 8.08,11.24Hz, H_e);6.50-6.54(d, 1H, J= 15.92, H_f); 6.83- 7.04 (m, 3H, Thiophene ring); 7.13-7.53 (m, 4H, phenyl ring), ^{13}CNMR (200$MH_Z$$CDCl_3$): δ 44.52, 84.98, 115.55, 123.0, 124.8, 127.21,128.52, 137.99, 162.20, 164.97, Mass Spectrum: m/z 247M^+, CHN calculated: C 63.14, H 4.08, N 5.66, CHN found : C 63.12, H 4.06, N 5.64

Preparation of 5-(4-nitrophenyl)-3-(thiophen-2-yl)-4,5-dihydroisoxazole:**3e**: $C_{13}H_{10}N_2O_3S$
Yield: 90%, Melting Point: 118° C, IR (KBr, λ_{max}/cm^{-1}): 1674(C=N), 1109 (C-O), 2450(CH_2 iso)cm^{-1}, ^{1}H NMR(400 MHz, $CDCl_3$ /DMSO-d6): δ(ppm) 2.49-2.56 (dd, 1H, J=8.16,11.32Hz,H_d);2.03-2.10(dd, 1H, J=8.2, 11.24Hz, H_e)7.05-7.09 (d,1H, J= 14.24Hz, H_f); 7.3-7.9(m, 3H, Thiophene ring);7.82 -8.29 (m, 4H, phenyl ring),^{13} C NMR (200MH_Z $CDCl_3$) : δ42.59, 83.45, 124.09,125.81,127.99,129.50,146.55,148.22, 164.21, Mass Spectrum: m/z 275M^+,CHN calculated: C 56.92, H 3.67, N 10.21, CHN found : C 56.90 ,H 3.65,N 10.19

III. Results and Discussion

Primarily **1a** was desired as a model substrate. We have optimized the reaction conditions in a variety of solvents at diverse time intervals. **1a** was subjected to reaction with hydroxylamine hydrochloride to afford 3-(thiophen-2-yl)-5-p-tolyl-4,5-dihydroisoxazole (**3a)**. (Scheme 1, Table 1)

SCHEME 1: Synthesis of **Thiophene isoxazolines**

Table 1: Optimization of the reaction conditions for the synthesis of 3-(thiophen-2-yl)-5-p-tolyl-4,5-dihydroisoxazole (3a)

Entry	Solvent	Temp	% of isolated yield at time interval					
			1 h	2 h	3 h	4 h	5h	6h
1	AcOH (S_1)	Reflux	25	40	50	62	70	80
2	AcOH/water (S_2)	Reflux	20	30	45	55	60	72
3	DMF (S_3)	Reflux	15	25	35	40	45	45
4	DMF/water (S_4)	Reflux	11	20	30	30	35	35
5	[bmim][BF_4] (S_5)	80°	30	50	60	70	75	90
6	[bmim][BF_4]/water (S_6)	80°	20	40	50	65	80	90
7	[bmim][BF_4]/water/ AcOH (S_7)	80°	50	60	95	95	95	95

We have executed the optimization model, which was earlier reported in the synthesis of pyrimidine-isoxazolines in our laboratory by K. Lanjewar et al[21].The reaction of **1a** and hydroxylamine hydrochloride in ethanol with $\mathbf{S_1}$ at reflux was complete within 6 h, giving **3a** in 80% isolated yield. The progress of the reactions was checked in every one hour ranging from 1to 6 h. TLC was not feasible as the reaction mixture contained ionic liquid. The reaction time was vigilantly controlled to avoid the breakup of products and formation of byproducts. It was examined that the reaction not proceeded well by addition of a small amount of water, the yield was reduced to 72%. The efficency the of reaction was noticeably influenced by the nature of solvents, when we increased the hydrophilicity of the reaction mixture $\mathbf{S_2}$ which reduced the outcome of the product. Additionally, reaction in DMF $\mathbf{S_3}$ and DMF /water $\mathbf{S_4}$ at reflux for 6 h reduced the yield drastically. In $\mathbf{S_3}$ and $\mathbf{S_4}$, the yield obtained was highly reduced, this suggested that the reaction rate may enhanced in protoic solvents. Furthermore, the reactions in ionic liquid [bmim][BF_4] $\mathbf{S_5}$, [bmim][BF_4]/water $\mathbf{S_6}$, [bmim][PF_6]/water/AcOH $\mathbf{S_7}$ were monitored at 80°C after various time intervals. The reaction takes place at 70°C in ionic liquids $\mathbf{S_5}$-$\mathbf{S_7}$. The use of [bmim][BF_4]/water/AcOH $\mathbf{S_7}$ demonstrated in much elevated reaction rates than those performed with $\mathbf{S_5}$-$\mathbf{S_6}$ solvent systems. Remarkably, it was observed that the reaction of **3a** proceeds better in all ionic liquids as compared to common organic solvents $\mathbf{S_1}$-$\mathbf{S_4}$. Reaction in $\mathbf{S_7}$ conclusively proved the utmost level of efficacy and atom economy when compared to solvents S_1-S_4. On top, use of AcOH/water as the secondary solvents in $\mathbf{S_7}$ illustrated the enhance productivity of the reaction. As a result, the reaction exercised well in acidic and protic solvents, additionally the use of ionic liquid augmented the outcome of the reaction. Table 1. summarizes our results, clearly showing the superiority of ionic liquid/AcOH/water biphasic system over organic solvent-water system.

The track of the reaction was monitored by TLC but we found that for all early experiments, TLC or HPLC was not an optimal choice for evaluation of yields or for a quantitative in-process assay; the viscous solution containing water and ionic liquids was not conductive to TLC. We resorted to quenching the reaction by adding little amount of water and moreover the product was isolated by extraction with Et_2O in 4 installments. The ionic liquid was kept over at $CaCl_2$ in the dessicator and furthermore it was oven dried prior to reuse for next cycle of reaction. The elemental analysis was conducted on isolated compounds and yields were calculated on purified compounds.We searched our investigation to new substrates by varying the substituents on ring B Table 2.

Table: 2 Characterization and physical contant of 3-(thiophen-2-yl)-5-p-tolyl-4,5-dihydroisoxazole **(3a-e)**

Entry	Compd.	R	Yield[a] (%)	m.p. (^{O}C)
1	**3a**	CH_3	95	123
2	**3b**	Br	92	117
3	**3c**	Cl	95	127
4	**3d**	F	95	161
5	**3e**	NO_2	90	118

In Table 2, it was observed that, the incorporation of electron withdrawing substituents at the para position of ring B (Scheme 1) (entries 4b-e) did not exhibited any noticable change in yield.

To authenticate the effect of concentration of [bmim][BF_4] on the efficiency of the reaction, we progressively increased the concentration of [bmim][BF_4]/water from 1 mmol-15 mmol keeping 10 mmol of water and acetic acid constant at 80^{o}C for 3 h. It was observed that as the concentration of [bmim][BF_4] in water/acetic acid increased, the efficiency of the reaction also increased. On completion, variations in yields were observed, encouraged us to repeat this procedure a number of times; proving that variations in yield were not attributeable to work-up losses. Beyond 10 mmol of [bmim][BF_4] the efficiency was decreased, suggesting that the acidic, polar and hydrophilic environment was conducive to the reaction and excess amount of ionic liquid may interfere the reaction mechanism. Reasonable hydrophobic-hydrophilic solvent interactions have been observed.

A plausible explanation of the reaction mechanism[21] in ionic liquid-water biphasic system is as follows:1-butyl-3-methyl imidazolium tetra fluoroborate [bmim][BF_4] is hydrophilic and miscible with water. One of the reactants **3a** is hydrophobic while hydroxylamine hydrochloride is hydrophilic in nature. Non polar end of the ionic liquid may show affinity towards hydrophobic moiety which enhances the rate of the reaction. Different solvation affinities of these two reactants may be resoluted at in situ solvent system. $\mathbf{S_7}$ solvent system provides a platform in which the non polar organic counterpart $[bmim]^+$ easily makes **3a** soluble; $[BF_4]^-$ water counterpart makes hydroxylamine hydrochloride soluble. The hydroxylamine hydrochloride in aqueous phase is transported to ionic liquid phase where reaction occurs at in situ solvent system Figure 1. This suggests that IL biphasic system effectively delivers the products in homogeneous solvent system.

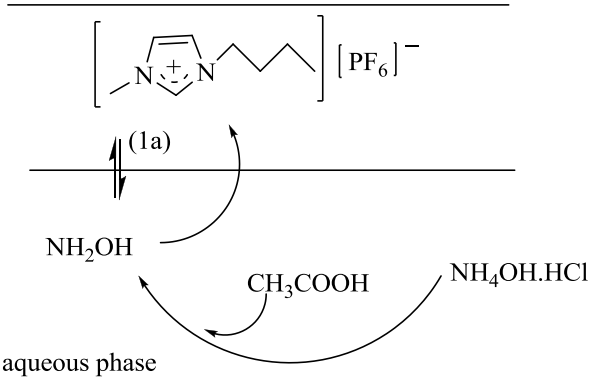

FIGURE 1 A plausible mechanism in ionic liquid-water biphasic system[21]

On completion of the reaction, we have optimized the extraction and isolation of the resulting product in ionic phase by using various solvents such as diethyl ether, di-chloromethane, ethyl acetate and n-hexane; the best results were obtained with diethyl ether and this was the solvent of choice for further experiments. Inorganic salts, formed as byproduct dissolved in water. The separated ionic liquid was flushed out with diethylether. The excess amount of water was removed by keeping the ionic liquid in $CaCl_2$ dessicator. The oven dried ionic liquid was reused for next cycle, without diminution of the yields up to the 10 cycle but there is noticeable drop in yield after 10th cycle suggested that the catalyst may have contaminated or degraded or

exhausted. This procedure has the merit of being environmentally benevolent possessing effortless operation, expedient work-up, reduced time and proceeding in good yields.

For elucidation of the structure **3a-e**, in Table 2 the IR spectra showed a peak at 1657 cm^{-1} due to C=N stretching of pyrazoline ring, peak at 1097 cm^{-1} because of C-O stretching of isoxazoline ring respectively. Furthermore ^{1}H NMR spectra of compounds **3a-e** showed a singlet of 3 protons at δ 2.45 due to Ar-CH_3 protons. In isoxazoline ring, there are three types of hydrogens, one attached to C_3 carbon ie H_3 and (H_1 and H_2) two at C_4 carbon of isoxazoline ring. The two hydrogens attached to C_4 position are juxtaposed cis and trans $H_1$and H_2. ^{1}H NMR spectra showed for H_3, dd at δ 7.00-7.02 due to H_2 proton and H_1. H_2 coupled with both H_1 and H_3 to give a dd at δ 2.50-2.51 . The dd at δ 2.35-2.40 due to H_3 and H_2 proton, confirmed the structure of isoxazoline ring. The ^{13}C NMR spectra also support the structure; signals at δ 21, 42, 83, 124 and 161 indicate the presence of isoxazoline ring. Compounds **3a-e** gave satisfactory elemental analysis; mass spectra also lend credence to the structures.

Stereochemical aspects: To reveal the steriospecificity of the compounds, they were tested for specific rotation. It was observed that all the compounds were found to be optically inactive with no specific rotation. Thus we have not atempted to resolve the chiral centres: this was refered to later date pending obtaintion of possible activity and subsequent optimization.

The purity of the compounds was monitored by TLC and the structures of all the derivatives **3a-e** were supported by spectral data. The IR, ^{1}HNMR, ^{13}CNMR, Mass spectra and elemental analytical data are in agreement with the proposed structures. Physical and analytical data of the synthesized compounds are reported in Table 2.

IV. Conclusion

In conclusion, the ionic liquid [bmim][BF_4]/AcOH/water proved to be an remarkably proficient solvent system for the synthesis of isoxazolines at ambient temperature within 3 h. The reaction is influenced by [bmim][BF_4]/water/AcOH biphasic system which stabilizes the hydrophobic reactant, and water/AcOH stabilizes hydroxylamine hydrochloride: the reaction presumably occurs at homogeneous phase. The study was finally completed by performing their *in-vitro* anti-fungal activities of all compounds.

V. Acknowledgements

The authors wish to express their gratitute to University Grant Commission, New Delhi, for finanacial assistance to UGC Major Project,File No-37-497/2009(SR)dated:15/07/2010 and the Sophisticated Analytical Instrumentation Facility(SAIF), Chandigarh, for ^{1}H NMR, ^{13}CNMR, IR, and Mass spectroscopic analysis.

References

[1]. Giovannoni, M. P.; Vergelli, C.; Ghelardini, C.; Galeotti, N.; Bartolini, A.; DalPiaz, V. [(3-Chlorophenyl) piperazinylpropyl]pyridazinones and Analogues as Potent Antinociceptive Agents. J. Med. Chem., 2003, 46, 1055-1059.

[2]. Carlsen, L.; Do pp, D.; Do pp, H.; Duus, F.; Hartmann, H.; Lang-Fugmann, S.; Schulze, B.; Smalley, R. K.; Wakefield, B. J.; In Houben-Weyl Methods in Organic Chemistry; Schaumann, E., Ed.; Georg Thieme Verlag: Stuttgart, 1992; Vol. E8a, p 45-204.

[3]. Lee, Y.; Koyama, Y.; Yonekawa, M.; Tanaka, T. New Click Chemistry: Polymerization Based on 1,3-Dipolar Cycloaddition of a Homo Ditopic Nitrile N-Oxide and Transformation of the Resulting Polymers into Reactive Polymers. Macromolecules;2009, 42, 7709-7717.

[4]. O. A. Fathalla, S. M. Awad, and M. S. Mohamed, Synthesis of new 2-thiouracil-5-sulphonamide derivatives with antibacterial and antifungal activity. Arch. Pharm. Res., 2005, 28(11), 1205-1212.

[5]. K. Hemlata, K. Sunil and K. Ashok, Synthesis, Antipsychotic and Anticonvulsant Activity of some new pyrazolinyl/isoxazolinylindol-2-ones Chem. Tech., 2010, 2(2), 1010-1019.

[6]. B. R. Dravyakar, D. P. Kawade, P. B. Khedekar, and K. P. Bhusari, Design and syntheses of some new diphenylaminoisoxazolines as potent anti-inflammatory agent. Ind. J. Chem., 2008, 47B, 1559-1567.

[7]. P. Paola, N. Monica, L. Manuela, M. Annamaria, C. Valeria, A. Alessandra, R. Michele, S. Daniele, and D. Natzle,: The antitumor activities of curcumin and of its isoxazole analogue are not affected by multiple gene expression changes in an MDR model of the MCF-7 breast cancer cell line: Analysis of the possible molecular basis, Int. J. Mol. Med., 2007, 20, 329-335.

[8]. T. Karabasanagouda, V. A. Airody, and M. Girish, Synthesis of some new pyrazolines and isoxazoles carrying 4-methylthiophenyl moiety as potential analgesic and anti-inflammatory agents. Ind. J. Chem., 2009, 48B, 430-437.

[9]. K. Hiroyuki, I. Tsuneo, O. Toshikazu, T. Akira, and M. Michio, J. Pestic. Sci., 2000, 25, 240.

[10]. . Ebraheem Abdu Musad,Riyaz Mohamed,Bahjat Ali Saeed,Bannikuppe S. Vishwanath,K. M.Lokanatha Rai,: Synthesis and evaluation of antioxidant and antibacterial activities of new substituted bis(1,3,4-oxadiazoles), 3,5-bis(substituted) pyrazoles and isoxazoles, Bioorganic & Medicinal Chemistry Letters,21 (2011) 3536–3540

[11]. Y. S. Hae, J. L. Eun, E. L. Jie, P. Woo-Kyu, B. Du-Jong, S. C. Yong, Y. K. Hun, C. Hyunah, and N. P. Ae, Synthesis and Biological Evaluation of Isoxazoline and Isoxazole Derivatives as 5-HT2A and 5-HT2C Receptor Ligands. Bull. Korean Chem. Soc., 2009, 30(8), 1873-1876.

[12]. S. B. Jadhav, R. A. Shastri, K. V. Gaikwad, and S. V. Gaikwad,: Synthesis and Antimicrobial Studies of Some Novel Pyrazoline and Isoxazoline Derivatives, fur. J. Chem., 2009, 6(S1), S183-S188.

[13]. (a) Valizadeh, H.; Amiri, M.; Gholipur, H.:Efficient and convenient method for the synthesis of isoxazoles in ionic liquids,J. Heterocyclic Chem.; 2009, 46, 108-110. (b) Tang, S.; He, J.; Sun, Y.; He, L.;She, X.:Efficient and Regioselective One-Pot Synthesis of 3-Substituted and 3,5-Disubstituted Isoxazoles,Org. Lett.; 2009, 11, 3982-3985.

[14]. Denmark, S. E.; Kallemeyn,: Synthesis of 3,4,5-Trisubstituted Isoxazoles via Sequential [3 + 2] Cycloaddition/Silicon-Based Cross-Coupling Reactions,J. M. J. Org. Chem. 2005, 70, 2839–2842. (b) Hansen, T. V.; Wu, P.; Fokin, V. V. ; One-Pot Copper(I)-Catalyzed Synthesis of 3,5-Disubstituted Isoxazoles,J. Org. Chem.;2005, 70, 7761–7764.
[15]. Grecian, S.; Fokin, V. V. : Ruthenium- Catalyzed Cycloaddition of Nitrile Oxides and Alkynes: Practical Synthesis of Isoxazoles,Angew.Chem., Int. Ed.,2008, 47, 8285.
[16]. T. Welton, Room temperature ionic liquids: Solvents for synthesis and catalysis, Chem. Rev. 99 (1999) 2071–2084
[17]. J. Gorman, Faster, better, cleaner? New liquids take aim at old-fashioned chemistry, Sci. News 160 (2001) 156–158.
[18]. Manthiriyappan, S. ; Lee, C. K.:Biocatalytic reaction in hydrophobic ionic liquids,Journal of Molecular Catalysis B: Enzymatic, 60(1-2):1-12 ,2009
[19]. Vitaly V. Chaban ,Oleg V. Prezhdo: How toxic are ionic liquids/Acetonitrile mixtures?,J. Phys. Chem. Lett., 2011, 2 (19), pp 2499–2503.
[20]. Shapi ,A; Siddiqui, U. C. Narkhede, S. S.; Palimkar, T. D; Rajgopal, J. L; Kumar, V. S. Room temperature ionic liquid promoted improved and rapid synthesis of 2,4,5-triaryl imidazoles from aryl aldehydes and 1,2-diketones or α-hydroxyketone. Tetrahedron,2005, 61 3539–3546.
[21]. K. Lanjewar, A. Rahatgaonkar, M. Chorghade and Saraf, B., Facile Synthesis of Pyrimidine-Isoxazoline Hybrids in [bmim][PF6]-Water Biphasic System. Synthesis,16, 2644, (2011).

Priyanka C. Burde "Synthesis Of Thiophene Isoxazolines In Ionic Liquid [Bmim][BF_4]." IOSR Journal of Applied Chemistry (IOSR-JAC) 11.4 (2018): 57-62.